Paper Alert

Chosen by Robert Liddington[1] and Christin Frederick[2]

A selection of interesting papers that were published in the month before our press date in major journals most likely to report significant results in structural biology.

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Structure 1996, Vol 4 No 12:1531–1534

□ Three-dimensional structures of HIV-1 and SIV protease product complexes. Robert B Rose, Charles S Craik, Nancy L Douglas and Robert M Stroud (1996). *Biochemistry* 35, 12933–12944.

HIV protease, essential to the life-cycle of the human immunodeficiency virus (HIV), processes eight cleavage sites of the viral gag and gag-pol polyproteins. The mechanism involves acid–base hydrolysis mediated by two catalytic aspartic acid residues. The authors describe the first structures of product complexes of aspartyl proteases with HIV-1 and simian immunodeficiency virus (SIV) proteases. The eight complexes include two N-terminal and two C-terminal product complexes. Modeling the substrate from the products indicates that substrates bind to the active site without strain. A chemical mechanism for HIV protease is proposed based on models for the Michaelis complex and gemdiol intermediate.
1 October 1996, *Biochemistry*

□ A model of the iron responsive element RNA hairpin loop structure determined from NMR and thermodynamic data. Lance G Laing and Kathleen B Hall (1996). *Biochemistry* 35, 13586–13596.

The iron responsive element (IRE) is a conserved RNA structure that is found in the 5' untranslated region (UTR) of ferritin mRNA and in the 3' UTR of transferrin receptor mRNA. It is the binding site of the iron responsive protein (IRP), and the interaction is part of the regulation of cellular iron metabolism. The IRE six-nucleotide hairpin loop, $5'C_1A_2G_3U_4G_5N_6$, is required for IRP binding. Measurements of loop stability show that it has 2.9 kcal mol^{-1} more free energy than predicted. NMR data suggest that there is hydrogen bonding between C1 and G5 in a tertiary interaction across the loop analogous to that seen in stable tetraloop structures.
22 October 1996, *Biochemistry*

□ Solution structures of 5-fluorouracil-substituted DNA and RNA decamer duplexes. Parag V Sahasrabudhe, Richard T Pon and William H Gmeiner (1996). *Biochemistry* 35, 13597–13608.

The nucleoside antimetabolite 5-fluorouracil (FUra) is the principal chemotherapeutic agent used clinically in the treatment of solid tumors, particularly for gastrointestinal malignancies. The structures in solution of eight oligonucleotide duplexes each containing either zero, one, or two 5-fluorodeoxyuridine (FdUrd) or 5-fluorouridine (FUrd) nucleosides were determined by NMR. FdUrd substitution affects the base roll angle at the site of FdUrd substitution, causing the helical axis of substituted DNA duplexes to bend. A–FUrd base pairs show substantial deviations from A–Urd base pairs in all three of the RNA duplexes substituted with FUrd.
22 October 1996, *Biochemistry*

□ Three-dimensional structure of ***meso***-diaminopimelic acid dehydrogenase from ***Corynebacterium glutamicum.*** Giovanna Scapin, Sreelatha G Reddy and John S Blanchard (1996). *Biochemistry* 35, 13540–13551.

Diaminopimelate dehydrogenase catalyzes the NADPH-dependent reduction of ammonia and L-2-amino-6-ketopimelate to form *meso*-diaminopimelate, the direct precursor of L-lysine in the bacterial lysine biosynthetic pathway. The 2.2 Å crystal structure of the binary complex of the enzyme with $NADP^+$ reveals a homodimer composed of three domains. The relative position of the N- and C-terminal domain in the two monomers is different, defining an open and a closed conformation that may represent the enzyme's binding and active state, respectively.
22 October 1996, *Biochemistry*

■ Crystal structure of a σ^{70} subunit fragment from ***E. coli*** RNA polymerase. Arun Malhotra, Elena Severinova and Seth A Darst (1996). *Cell* 87, 127–136.

The 2.6 Å crystal structure of a fragment of the σ^{70} promoter specificity subunit of *Escherichia coli* RNA polymerase is described. Residues involved in core RNA polymerase binding lie on one face of the structure. On the opposite face, aligned along one helix, are exposed residues that interact with the –10 consensus promoter element (the Pribnow box), including four aromatic residues involved in promoter melting. The structure suggests one way in which DNA interactions may be inhibited in the absence of RNA polymerase.
4 October 1996, *Cell*

■ See review by Chan, Lonetto and Gross in the 15 November issue of *Structure* (Volume 4:1235–1238).

☐ Structure of the C-terminal region of $p21^{WAF1/CIP1}$ complexed with human PCNA. Jacqueline M Gulbis, Zvi Kelman, Jerard Hurwitz, Mike O'Donnell and John Kuriyan (1996). *Cell* 87, 297–306.

The protein $p21^{WAF1/CIP1}$ is an inhibitor of the cyclin-dependent protein kinases (cdks) that control the initiation of the S phase of the cell cycle and concomitant DNA replication. The crystal structure of the human DNA polymerase δ processivity factor PCNA (proliferating cell nuclear antigen) complexed with a 22 residue peptide derived from the C terminus of $p21^{WAF1/CIP1}$ has been determined at 2.6 Å resolution. p21 binds to PCNA in a 1:1 stoichiometry with an extensive array of interactions that include the formation of a β sheet with the interdomain connector loop of PCNA. An intact trimeric ring is maintained in the structure of the p21–PCNA complex, with a central hole available for DNA interaction.
18 October 1996, *Cell*

☐ The crystal structure of hepatitis C virus NS3 proteinase reveals a trypsin-like fold and a structural zinc binding site. Robert A Love, Hans E Parge, John A Wickersham, Zdenek Hostomsky, Noriyuki Habuka, Ellen W Moomaw, Tsuyoshi Adachi and Zuzana Hostomska (1996). *Cell* 87, 331–342.

Hepatits C virus (HCV) is the major etiologic agent of non-A, non-B hepatitis. During replication of HCV, the final steps of polyprotein processing are performed by a viral proteinase located in the N-terminal one-third of nonstructural protein 3 (NS3). The structure of NS3 proteinase from HCV BK strain was determined by X-ray crystallography at 2.4 Å resolution. NS3P folds as a trypsin-like proteinase with two β barrels and a catalytic triad. Novel features include a structural zinc-binding site and a long N terminus that interacts with neighboring molecules by binding to a hydrophobic surface patch. (The structure of the protease in complex with synthetic activated peptide is described in the same issue: J.L Kim, K.A. Morgenstern, C.Lin, T.Fox, M.D. Dwyer, J.A. Landro, S.P. Chambers, W. Markland, C.A. Lepre, E.T. O'Malley, S.L. Harbeson, C.M. Rice, M.A. Murcko, P.R. Caron and J.A. Thomson, *Cell* 87, 343–355.)
18 October 1996, *Cell*

☐ Crystal structure of enoyl-coenzyme A (CoA) hydratase at 2.5 Å resolution: a spiral fold defines the CoA-binding pocket. Christian K Engel, Magali Mathieu, Johan Ph Zeelen, J Kalervo Hiltunen and Rik K Wierenga (1996). *EMBO J.* 15, 5135–5145.

Enoyl-coenzyme A (CoA) hydratase catalyzes the reversible addition of water to α,β-unsaturated enoyl-CoA thioesters. The crystal structure reveals a hexamer (mw 161 kDa). The monomer is folded into a right-handed spiral of four turns, followed by two small domains which are involved in trimerization. The active-site architecture confirms the importance of two glutamic acid residues in the catalytic mechanism.
1 October 1996, *The EMBO Journal*

☐ Crystal structure of NH_3-dependent NAD^+ synthetase from ***Bacillus subtilis.*** Menico Rizzi, Claudio Nessi, Andrea Mattevi, Alessandro Coda, Martino Bolognesi and Alessandro Galizzi (1996). *EMBO J.* 15, 5125–5134.

NAD^+ synthetase catalyzes the last step in the biosynthesis of nicotinamide adenine dinucleotide. The crystal structure reveals a tight homodimer with α/β subunit topology. The catalytic site is located at the parallel β sheet topological switch point. Implications for the catalytic mechanism are discussed.
1 October 1996, *The EMBO Journal*

☐ 2.5 Å resolution crystal structure of the motile major sperm protein (MSP) of ***Ascaris suum.*** Timothy L Bullock, Thomas M Roberts and Murray Stewart (1996). *J. Mol. Biol.* 263, 284–296.

The crystal structure of the *Ascaris* major sperm protein (MSP) is described at 2.5 Å resolution. The MSP polypeptide chain has an immunoglobulin-like fold which most closely resembles that of the N-terminal domain of the bacterial chaperonin, PapD. In the crystal, two MSP chains are tightly associated into a dimer. Additional crystal contacts suggest a mode for the assembly of MSP into the filaments which promote cell movement. This dimer–dimer association resembles the interaction between PapD and its protein substrate.
25 October 1996, *Journal of Molecular Biology*

☐ Structure of a unique binuclear manganese cluster in arginase. Zoltan F Kanyo, Laura R Scolnick, David E Ash and David W Christianson (1996). *Nature* 383, 554–557.

Arginase catalyzes the hydrolysis of arginine, the final cytosolic step of the urea cycle. Arginase requires a spin-coupled Mn^{2+}–Mn^{2+} cluster for catalytic activity. The 2.1 Å-resolution crystal structure of trimeric rat liver arginase reveals that this unique metal cluster resides at the bottom of an active-site cleft that is 15 Å deep. Analysis of the structure indicates that arginine hydrolysis is achieved by a metal-activated solvent molecule which symmetrically bridges the two Mn^{2+} ions.
10 October 1996, *Nature*

☐ Structure of a replication-terminator protein complexed with DNA. Katsuhiko Kamada, Takashi Horiuchi, Katsufumi Ohsumi, Nobuo Shimamoto and Kosuke Morikawa (1996). *Nature* 383, 598–603.

The crystal structure of the *Escherichia coli* replication-terminator protein (Tus) bound to terminus-site (*Ter*) DNA has been determined at 2.7 Å resolution. The Tus protein folds into a previously undescribed architecture divided into two domains by a central basic cleft. This cleft accommodates locally deformed B-form *Ter* DNA and makes extensive contacts with the major groove, mainly through two interdomain β strands. The unusual structural features of this complex may explain how the replication fork is halted in only one direction.
17 October 1996, *Nature*

☐ Domain swapping creates a third putative combining site in bovine odorant binding protein dimer. Mariella Tegoni, Roberto Ramoni, Enrico Bignetti, Silvia Spinelli and Christian Cambillau (1996). *Nat. Struct. Biol.* 3, 863–867.

In mammals, odorant binding proteins may play an important role in the transport of odors towards specific olfactory receptors on sensory neurones across the aqueous compartment of the nasal mucus. The authors have solved the X-ray structure of such a transport protein, bovine odorant binding protein (OBP) at 2.0 Å resolution. The β barrel of OBP is similar to that of lipocalins, but OBP dimer association results from domain swapping. An open cavity is located at the dimer interface. Data in solution suggest that this central cavity may be a binding site created by domain swapping.
October 1996, *Nature Structural Biology*

☐ Three-dimensional structure of human cyclin H, a positive regulator of the CDK-activating kinase. Kyeong Kyu Kim, Holly M Chamberlin, David O Morgan and Sung-Hou Kim (1996). *Nat. Struct. Biol.* 3, 849–855.

Cyclin-dependent kinases (CDKs), which play a key role in cell cycle control, are activated by the CDK activating kinase (CAK), which activates cyclin-bound CDKs by phosphorylation at a specific threonine residue. Vertebrate CAK contains two key components: a kinase subunit with homology to its substrate CDKs and a regulatory subunit with homology to cyclins. The authors have determined the X-ray crystal structure of the regulatory subunit of CAK, cyclin H, at 2.6 Å resolution. Cyclin H contains two α-helical core domains with a fold similar to that of cyclin A, a regulatory subunit of CAK substrate CDK2, and of TFIIB, a transcription factor. Outside of the core domains, the N- and C-terminal regions of the three structures are completely different.
October 1996, *Nature Structural Biology*

☐ Elongation factor TFIIS contains three structural domains: solution structure of domain II. Paul E Morin, Donald E Awrey, Aled M Edwards and Cheryl H Arrowsmith (1996). *Proc. Natl. Acad. Sci. USA* 93, 10604–10608.

Transcription elongation by RNA polymerase II is regulated by the general elongation factor TFIIS. Yeast TFIIS is composed of three structural domains, termed I, II, and III. The two C-terminal domains (II and III) are required for transcription activity. This paper describes the NMR-derived structure of domain II: a three-helix bundle built around a hydrophobic core composed largely of three tyrosines protruding from one face of the C-terminal helix. The arrangement of known inactivating mutations of TFIIS suggests that two surfaces of domain II are critical for transcription activity.
1 November 1996, *Proceedings of the National Academy of Sciences USA*

☐ An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR–MHC complex. K Christopher Garcia, Massimo Degano, Robyn L Stanfield, Anders Brunmark, Michael R Jackson, Per A Peterson, Luc Teyton and Ian A Wilson (1996). *Science* 274, 209–219.

The central event in the cellular immune response to invading microrganisms is the specific recognition of foreign peptides bound to major histocompatibility complex (MHC) molecules by the αβ T cell receptor (TCR). The crystal structure of the complete extracellular fragment of αβ TCR was determined at 2.5 Å. The TCR resembles an antibody in the variable Vα and Vβ domains but deviates in the constant Cα domain and in the interdomain pairing of Cα with Cβ. The TCR combining site is relatively flat except for a deep hydrophobic cavity between the hypervariable complementarity determining regions (CDR3s) of the α and β chains. The structure of the TCR–MMC–peptide complex was elucidated from co-crystals of the complex.
11 October 1996, *Science*

☐ Crystal structure of DNA recombination protein RuvA and a model for its binding to the Holliday junction. John B Rafferty, Svetlana E Sedelnikova, David Hargreaves, Peter J Artymiuk, Patrick J Baker, Gary J Sharples, Akeel A Mahdi, Robert G Lloyd and David W Rice (1996). *Science* 274, 415–421.

The *Escherichia coli* DNA binding protein RuvA acts in concert with the helicase RuvB to drive branch migration of Holliday intermediates during recombination and DNA repair. The crystal structure of RuvA was determined at a resolution of 1.9 Å. Four monomers of RuvA are related by fourfold symmetry in a manner reminiscent of a four-petalled flower. The four DNA duplex arms of a Holliday junction can be modeled in a square planar configuration and docked into grooves on the concave surface of the protein around a central pin that may facilitate strand separation during the migration reaction. The model presented reveals how a RuvAB–junction complex may also accommodate the resolvase RuvC.
18 October 1996, *Science*

☐ Crystal structure of the ternary complex of 1,3,8-trihydroxynaphthalene reductase from ***Magnaporthe grisea*** with NADPH and an active-site inhibitor. Arnold Andersson, Douglas Jordan, Gunter Schneider and Ylva Lindqvist (1996). *Structure* 4, 1161–1170.

The enzyme 1,3,8-trihydroxynaphthalene reductase (THNR) is the target of several commercially important fungicides which are used to prevent blast disease in rice plants. The crystal structure reveals a dinucleotide-binding fold. Four subunits form a tetramer with *222* symmetry. Tricyclazole, an inhibitor of the enzyme, binds at the active site in the vicinity of the NADPH nicotinamide ring. The active site contains a Ser-Tyr-Lys triad which is proposed to participate in catalysis.
15 October 1996, *Structure*

□ Helix unwinding in the effector region of elongation factor EF-Tu–GDP. Galina Polekhina, Søren Thirup, Morten Kjeldgaard, Poul Nissen, Corinna Lippmann and Jens Nyborg (1996). *Structure* **4**, 1141–1151.

The previously determined structure of the GDP form of EF-Tu is known only as a trypsin-modified fragment, which lacks the Switch I, or effector, domain. This paper reports the crystal structures of intact EF-Tu–GDP from *Thermus aquaticus* and *Escherichia coli*. The C-terminal part of the effector region of EF-Tu–GDP is a β hairpin; in EF-Tu–GTP, this region forms an α helix. This change is presumably involved in triggering the release of tRNA and EF-Tu from the ribosome. (Similar results are reported by Kenton Abel, Marilyn D Roder, Rolf Hilgenfeld and Frances Jurnak, *Structure* **4**, 1153–1159.)

15 October 1996, *Structure*